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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,212	06/17/2005	Olga N. Kovbasnjuk	60384(71699)	2349

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EDWARDS ANGELL PALMER & DODGE LLP
Client: JHU
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
HUFF, SHEELA JITENDRA	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
05/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,212	KOVBASNJUK ET AL.	
	Examiner	Art Unit	
	Sheela J. Huff	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed on 4/22/08 has been considered. Applicant's arguments are deemed to be persuasive-in-part.

Claims 1-12 and 18 are pending.

The art rejection is withdrawn in favor of a new one.

Response to Arguments

Specification

The disclosure remains objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Applicant argues that the hyperlink has been replaced. It appears to be replaced with the exact same link and the link is still active.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 remains rejected because of the terminology "derived". Applicant argues that the American Heritage Dictionary definition states to obtain/receive from a source. Webster'sII New Riverside University Dictionary (1984) p. 365 states several definitions for this term and one include "to product of obtain...from another substance by chemical reaction". This reads on derivatizing. Applicant argues that they mean it to mean the term --obtained--. Replacing "derived" with --obtained-- will overcome this rejection.

Claims 1-9 and 11-12 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a method of reducing of inhibiting invasiveness and metastasis of tumor cells expressing Gb3, does not reasonably provide enablement for a method of reducing of inhibiting or preventing invasiveness and metastasis of tumor cells not expressing Gb3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons for this rejection are of record in the paper mailed 10/22/07.

There were two parts to this rejection--the part pertaining to "prevention" and the part pertaining to method of reducing of inhibiting or preventing invasiveness and metastasis of tumor cells not expressing Gb3. Applicant did not respond to the second

part. The part pertaining to "prevention" is withdrawn in view of its deletion from the above claims.

New Grounds of Rejection

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a method of reducing of inhibiting invasiveness and metastasis of tumor cells expressing Gb3, does not reasonably provide enablement for the prevention of invasiveness and metastasis of tumor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification clearly shows that the B-subunit of the Shiga Toxin can be used to inhibit or reduce invasiveness and metastasis of tumor cells expressing Gb3. The state of the art clearly discloses that the B subunit of the toxin binds to and is internalized into target cells expressing Gb3 (see page 1162, first column, last paragraph of Haicheur et al International Immunology vol. 15 p. 1161 (2003)).

With respect to the terminology "preventing" applicant has not shown that the B subunit of the toxin can prevent any disease. Prevention of cancer reads on cancer vaccines. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease, however, Essell (J. NIH Res. 1995 7:46) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly the last paragraph) and

further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p. 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". As a venture capitalist of the director of product development at a large pharmaceutical company and you're likely to get the same response." (p. 1 para 1).

Furthermore, Boon (Adv. Can. Res. 1992 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerate or at least depress the capability to respond against the tumor (p. 206, para 2).

Thus, in view of the contemporary knowledge in the art of the general lack of successful applications of vaccines for the prevention of human diseases as discussed above, as well as the unpredictability in the art pertaining to an immune response against in patients with large tumor burdens as discussed above, as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention as claimed.

Response to applicant's arguments

Applicant argues that the publications cited by the Examiner are outdates especially in view of the fact that there is one cancer vaccine on the market. While the field of cancer vaccines is evolving, it is clear that the vaccine on the market underwent rigorous and extensive testing before it became available. And just because one cancer vaccine works, do not automatically translate to all cancer vaccines working and does not provide correlation of applicant's inhibition data to prevention data.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaCasse et al Blood vol. 88 p. 1561 (1995) in view of Marcato et al Infection and Immunity vol. 70 p. 1279 (3/2002), Strockbine et al J. Bacteriology vol. 170 p. 1116 (3/98), Accession Number 2002:397002 (3/2002), Green US 2002/0081307 and applicant's admission on page 6, lines 1-2 of the specification.

LaCasse et al disclose treatment of human B cell lymphoma from bone marrow in mice using Shiga-like toxin 1 (see entire reference). The reference also discloses that the toxin was administered after the cancer is present (see p. 1562, middle of first column). On page 6 of the specification, applicant admits the toxins are known to bind to Gb3 expressing cells, therefore it is expected that the cells of the reference are Gb3 expressing cells. The toxin is administered before the spread of the tumor and therefore prior to metastasis.

This reference does not disclose the use of the B subunit of Shiga toxin 1 or 2 and the limitations of claims 2, 6, 8-9, 11-12 and 18.

Marcato et al discloses that it is the B subunit of the toxins (either Shiga toxin 1 or 2) that are responsible for the toxicity.

Strockbine et al discloses that Shiga-like toxin and Shiga Toxin are over 99% homologous and that the difference between the two resides in the A subunit (see abstract).

Green discloses that Shiga-like toxin (also called verotoxin) and Shiga toxin are commonly known and the selection of one or the other is within the purview of one skilled in the art and that either toxin can be used in mammals (this reads on humans). (see summary of invention).

Accession Number 2002:397002 discloses that Gb3 is a biomarker for colon tumor cells.

In view of the disclosure of Marcato et al that the toxicity resides in the B subunit of either toxin and because Shiga-like toxin and Shiga Toxin are over 99% homologous and the difference between the two resides in the A subunit and because selection of either is within the purview of one skilled in the art, it is obvious that one skilled in the art can used the B subunit from either toxin and expect the same results and thus it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the B subunit of either toxin in the treatment of the primary reference with the expected benefit of treating B cell lymphoma. Since it is known that the toxins bind Gb3 cells and since colon tumor cells express Gb3, it is obvious that the B subunit of the toxin can be used in the method of the primary reference. Furthermore, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be

used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). In view of this, it would have also been obvious to use other known cancer treatment, such as radiation or chemotherapeutic agents in combination with the B subunit to treat B cell lymphoma.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J. Huff whose telephone number is 571-272-0834. The examiner can normally be reached on Tuesday and Thursday from 5:30am to 1:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sheela J Huff/
Primary Examiner
Art Unit 1643

SJH